Citation:

Erkkila AT, Lehto S, Pyorala K, and Uusitupa MIJ. N-3 fatty acids and five-year risks of death and cardiovascular disease events in patients with coronary artery disease. *Am J Clin Nutr* 2003 July; 78 (1): 65-71.

PubMed ID: 12816772

Study Design:

Cohort

Class:

B - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To investigate whether a high proportion of n-3 fatty acids in serum lipids would be associated with reduced risks of death and coronary events in patients with established CAD.

Inclusion Criteria:

Finnish cohort of EUROASPIRE study with clinically-established CAD, aged <71 at time of admission to hospital in 1991-94. The subjects fell into one of the following four criteria: First elective or emergency coronary artery bypass grafting (CABG), first elective or emergency percutaneous transluminal coronary angioplasty (PCTA) but no previous CABG, first or recurrent acute myocardial infarction (AMI) but with no previous CABG or PTCA or admitted with symptoms compatible with acute myocarial ischemia (AMIA) but in whom the diagnosis of AMI could not be confirmed and who no previous CABG, PCTA, or AMI.

Exclusion Criteria:

None listed

Description of Study Protocol:

- Evaluate the associations of diet and serum lipid fatty acid composition with mortality and cardiovascular events during a five-year follow-up of patients with clinically-established CAD
- Identification to four diagnostic categories: CABG (N=109), PTCA (N=106), AMI (N=101) or AMIS (N=99)
- > Six months after hospitalization the following were performed:
    - Interview with demographic questionnaire, smoking status, drug use, years of

education
- Height, weight in light clothing without shoes to calculate BMI
- Waist circumference midway between the lower rib margin and iliac crest and hip circumference at the maximum circumference over the buttocks
- BP on the right arm with an automatic digital sphygmomanometer with the subject in a sitting position and after a five-minute rest
- Diagnosis of diabetes was made if previously confirmed by an MD or if plasma glucose concentration was equal to or >7mmol per L
- Food records were completed for four days (three week days and one weekend day) estimating the portions by comparison with portion sizes in a booklet. A clinical nutritionist documented the information and analysis was done using MICRO-NUTRICA software.
- Fasting blood samples were drawn in the morning after 12 hours of fasting and stored at -70^{o} C until analyzed. Except fresh serum was used for analysis of serum total and lipoprotein lipids. Standardized enzymatic methods were used for analysis of serum lipids.
- Endpoints included deaths from all causes, CVD, and CAD; non-fatal AMI; non-fatal stroke; CABG; and PTCA.

Data Collection Summary:

The food records were analyzed for total calories, total fat, saturated, monounsaturated and polyunsaturated fat, cholesterol, protein, carbohydrate, fiber and alcohol.

Blood was analyzed for LDL, HDL, cholesterol, triacylglycerol, glucose, cholesteryl esters, phospholipids and fatty acid methyl esters.

Description of Actual Data Sample:

285 men and 130 women with CAD, mean age 61 years, range 33-74 years.

Summary of Results:

During the five-year follow-up, 36 patients died, 21 had MIs, and 12 had strokes. The patients who died were significantly older at baseline than those who survived and had significantly higher serum TC, LDL-C and TG concentrations, as well as higher intakes of fat and saturated fat and lower intakes of fiber.

Fish intake was divided into three categories: No intake (0 grams per day), and below and above median consumption (57 grams per day). Fish intake tended to be associated with low risks of death and of the combined endpoint of CVD death, AMI or stroke.

High proportions of ALA, EPA and DHA in CEs tended to be associated with a low risk of death. The relative risks of death adjusted for CVD risk factors for subjects in the highest tertile of fatty acids in CEs compared with those in the lowest tertile were 0.33 (95% CI: 0.11, 0.96) for a-linolenic acid, 0.33 (0.12, 0.93) for EPA, and 0.31 (0.11, 0.87) for DHA (P for trend =0.063, 0.056, and 0.026, respectively). A high proportion of EPA in CEs was associated with a low risk

in CAD death.

Fish intake correlated with proportions of EPA (r=0.568, P<0.01) and DHA (r= 0.545, P<0.01) in serum CEs. Compared with no consumption, consumption of fish tended to be associated with a lower risk of death [1-57 grams per day, relative risk =0.50 (0.20, 1.28); >57 grams per day, relative risk =0.37 (0.14, 1.00); P for trend =0.059].

Author Conclusion:

The main finding of the present study is that proportions of ALA, EPA and DHA in serum CEs are associated with a reduction in the risk of all-cause mortality. The associations between EPA and DHA and the risk of death were confirmed by the reduced risk observed in the subjects who ate fish or who had high proportions of EPA and DHA in serum phospholipids. The associations of n-3 fatty acids with combined fatal and non-fatal CVD events were, however, not significant. In conclusion, ALA, EPA and DHA are nutritional factors that could potentially reduce the risk of death in patients with CAD. Furthermore, this benefit can be obtained through the intake of foods and without the intake of supplements.

Reviewer Comments:

Author noted that the size of the study cohort may have limited the power of the statistical analysis, and since virtually all the patients were taking cardiovascular drugs, this could have confounded the observed associations. Dietary intakes and serum lipid fatty acid profiles measured only at baseline, and it is possible that dietary changes may have occurred during the follow-up period.

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions		
1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	Yes
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	N/A

Validity Questions		
1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes

1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	**Were study groups comparable?**	Yes
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	Yes
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	Yes
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	No
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	Yes
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	N/A

4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	N/A
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	N/A
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	N/A
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	Yes
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	Yes
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	Yes
6.6.	Were extra or unplanned treatments described?	Yes
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	Yes
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes

7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
7.7.	Were the measurements conducted consistently across groups?	N/A
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
8.6.	Was clinical significance as well as statistical significance reported?	Yes
8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**	Yes
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**	Yes
10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	Yes